UNIVERSITATEA LUCIAN BLAGA DIN SIBIU

Doctoral school of Medicine
Field of doctoral studies: **Medicine**

Doctoral thesis

THE IMPORTANCE OF THE "OCULAR SURFACE DISEASE INDEX" QUESTIONNAIRE IN DRY EYE SYNDROME (summary)

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SIBIU2022

Contents

OVERVIEW

Dry eye syndrome, also known as keratoconjunctivitis sicca or keratitis sicca, is a condition with a multifactorial etiology of tears and the ocular surface that causes a series of symptoms and signs, more and more common in ophthalmological pathology.

The definition of dry eye syndrome according to the Society of Ocular Surface and Teardrop Film - Dry Eye Workshop II is: "*Dry eye is a multifactorial disease of the ocular surface characterized by a loss of tear film homeostasis and accompanied by ocular symptoms, in which instability and tear film hyperosmolarity, inflammation, damage to the ocular surface and neurosensory abnormalities play etiological roles*" (1). Dry eye disease it's one of the most common ocular comorbidities and may overlap with other causes of ocular surface disease, such as ocular allergy and meibomian gland dysfunction. Dry eye syndrome is a multifactorial disease whose outcome is malfunctioning of the tear film due to insufficient tear production or increased tear film evaporation, with potential damage to the ocular surface (2). Prevalence of dry eye syndrome increases with age. studies show a prevalence between 5-50% of the adult population (3).

It is a very common eye disease nowadays that affects daily activities by decreasing the quality of life due to its symptoms. It has also become a major public health problem due to the high costs of treatment (4).

A study conducted by the National Institute for Occupational Safety and Health shows that approximately 90% of people working on computers are affected by this syndrome. (5).

"Computer vision syndrome", also called digital eye fatigue, has been described by the American Optometry Association as a vision and eye problem seen in long-term users of computers, tablets and mobile phones. (6).

Computer use leads to decreased blink rate, incomplete blinking, faster evaporation of tears from the eye surface, and later dry eye syndrome. (7).

The purpose of this study was to sound the alarm in terms of establishing an early diagnosis, establishing the stage of the disease, establishing the etiological treatment and last but not least establishing the methods of prevention associated with this syndrome among people working on computers for several hours per day.

The aim of treatment is to eliminate eye discomfort and avoid aggravation of this pathology in this group of patients.

SUMMARY

THEORETICAL PART

The general part of the paper consists of chapters 1-5 and presents current theoretical issues related to the definition of dry eye syndrome, anatomy, epidemiology, pathophysiology and current diagnostic methods.

The general part of the paper is a synthesis of the literature, which aimed to browse and analyze the published literature in the field of diagnosis of dry eye syndrome and to create a perspective, but also to identify studies to support the chosen topic.

THE PERSONAL PART

The personal part of the paper consists of chapters 6-11. The study group consists of 52 subjects.

The study group includes patients with evaporative dry eye syndrome, without other associated ocular pathologies.

The inclusion criteria in the study and the methodology will be detailed in each chapter. The patients were examined by the same investigator.

Chapter 6 of the special part is represented by “Introduction” in which are presented some data about Dry Eye Syndrome such as: generalities, definition, risk factors, signs and symptoms of dry eye, as well as some data about dry eye syndrome in people who works at the computer.

Chapter 7 contains the “Purpose of the paper” and lists the topics that want to be covered during the research. The aim of this study was to evaluate the influence of computer use for more than 5 hours a day on the ocular surface, the symptoms of dry eye and to evaluate the effectiveness of treatment on the ocular surface, using various topical drugs (artificial tears).

Also, one of the objectives of our research was to correctly and completely assess the symptoms of dry eye syndrome, identify the relationship between ocular symptoms and diagnostic clinical tests in dry eye syndrome, find an optimal combination of diagnostic tests that are as minimal-invasive as possible, but at the same time provide the necessary information for a complete and correct diagnosis.

We analyzed the sensitivity and specificity of the Ocular Surface Disease Index (OSDI) questionnaire in the diagnosis of various forms of Dry Eye Syndrome and the possibility of using it as a screening tool for this pathology. Based on this questionnaire, we aimed to find out which are the most common symptoms experienced by patients in the study group, which are the environmental factors that most influence the symptoms, but also how the symptoms have an effect on daily activities.

Chapter 8 is entitled “Material and method”: 100 OSDI (Ocular Surface Disease Index) questionnaires were sent to employees of IT (information technology) companies, along with a questionnaire that included age, sex, smoker / non-smoker, the average number of hours spent in front of the computer / day, history of eye problems.

After completing the questionnaires, people with a score of OSDI> = with 13 were called to the consultation for inclusion in the study.

All patients were informed of the inclusion in the study, the frequency of consultations, the non-invasive nature of the investigative methods used was explained to them and the written agreement to participate was obtained according to the Helsinki Declaration on Human Subjects (WMA DECLARATION OF HELSINKI - ETHICAL PRINCIPLES). FOR MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS).

Also, all patients were informed about the free ophthalmological consultations and treatment throughout the study and the importance of following the treatment throughout this study.

After patient acceptance of inclusion in the study, they underwent an initial ophthalmologic consultation that included: history, determination of visual acuity with and without optical correction, biomicroscopy of the anterior pole with examination of the eyelids and anterior pole at the slit lamp, Schirmer I test , tear break-up time (T-BUT), determination of tear PH, posterior pole examination. All patients underwent an initial consultation in the morning, before going to work, followed by an ophthalmological consultation in the evening, after work. During the consultation carried out in the evening, the Schirmer I test, the T-BUT and the tear pH were performed. After this consultation, the patient was initiated treatment with artificial tears, with a dosage of 3 x 2 pic / zit for 30 days. The final consultation (control), performed in the evening, at 30 days of treatment consisted of: filling in the OSDI questionnaire, Schirmer I test, T-BUT, tear PH.

Out of the total number of patients, 52 patients were included, 39 women and 13 men, aged between 20-60 years, with an average of 36.38 years, smokers and non-smokers, working on the computer between 5 and 10 hours / day. , with OSDI Score> 13, no history of dry eye syndrome previously diagnosed. All patients had symptoms of dry eyes, sandy sensation in the eyes, eye discomfort, foreign body sensation in the eyes.

Chapter 3 also includes some notions about artificial tears and hyaluronic acid present in their composition.

Chapter 9 contains the results of the study, as well as the correlations between the different parameters investigated**.**

Of the 52 patients, 39 were women (F) and 13 were men (M). Patients were grouped into 4 age groups such as: 20 - 29, 30 - 39, 40 - 49, 50 - 59, the maximum frequency was in the age group 40 - 49, and the lowest frequency in the age group 50 - 59. The average number of patients by age group was 36.38. The Kruskal-Wallis test was used to correlate different parameters with the age groups in which patients were placed. The values p> 0.05 show us that there are no significant differences between the values of the investigation methods used and the 4 age groups.

Of the total patients, 37 (71.15%) were non-smokers and 15 (28.85%) smokers. Correlations were made between the values of the variables for smokers and the values for non-smokers. Using the Mann-Whiteney Test, the values p> 0.05 show us that there are no significant differences between smokers / non-smokers.

The average number of hours spent on the computer was 7.67, with a standard deviation of 1.08. The 1-month OSDI score is directly correlated, insignificant (p=0.202) and weak with the number of hours spent at the computer (rho=0.180).

For OSDI Score A, which assesses SOU-specific ocular symptoms that occurred in the week before the consultation (light-sensitive eyes, sandy sensation in the eyes, eye burns, blurred vision, blurred vision), the initial values have an average of 8, 75, and the control values have an average of 5.33. A significant decrease in OSDI A score was observed at one month of treatment, which indicates a significant improvement in dry eye symptoms after 30 days of treatment in the patients included in the study.

OSDI B score brings us information on the visual function in carrying out daily activities (reading, driving at night, working on the computer, watching TV). The initial values have an average of 6.52, and the values after one month of treatment have an average of 4.02. A significant decrease in OSDI B score was observed at one month of treatment, which indicates a better performance of daily activities by patients.

The C OSDI score attempts an assessment of environmental factors (wind, locations or dry areas, computer work) as factors favoring dry eyes. The average of the initial C score was 5.79, and the average of the C score at control was 3.27.

The control C score had values by 2.52 lower compared to the initial C score, which suggests a decrease in eye discomfort under topical treatment in inappropriate environmental conditions.

OSDI D score represents the sum of all scores obtained in scores A, B, C. According to the results of each OSDI score, we observe a very large difference in the average of the initial D score (21.25) compared to the average of the control D score (12.63) .

The total OSDI score varies from 0 to 100. Scores from 0 to 12 represent normal values, values between 13 and 22 represent a mild form of SOU, between 23 and 32 represent a moderate form of SOU, and values higher than 33 represent a severe form of dry eye.
The total score is calculated based on the following formula: OSDI score = the sum of the scores for all questions answered (D) × 25 / total number of questions answered (E).

Out of the total number of patients enrolled in the study, 5 patients presented OSDI score values between 13 and 22, representing a mild form of SOU, 10 patients were in the average form of SOU, with scores between 23-32, and 37 were presented severe form of dry eye.

The minimum values of the OSDI score were 14.28, and the maximum value found was 87.50, and the average OSDI score was 44.86. Analyzing the results of the OSDI control score, a minimum score value of 10.41 was observed.

Post-treatment 4 patients had OSDI score below 13, 18 had results between 13-22, 12 were classified with moderate dry eye form, and 18 in severe dry eye form. The values obtained at the control have much lower values than the initial measurements.

Comparisons between initial and one-month OSDI measurements were made with the Wilcoxon Signed Ranks Test, and the results conclude that all values performed at 1 month of treatment are significantly lower than the initial measurements ($p<0.001$).

The initial OSDI score is directly correlated, significant ($p<0.001$) and strongly with the initial A score (rho = 0.814), the initial B score (rho=0.787), the initial C score (rho=0.814) and the initial D score (rho=0.980).

The initial OSDI score is directly correlated, insignificant ($p=0.179$) and weak with the number of hours spent at the computer (rho=0.189).

The 1-month OSDI score is directly correlated, significant ($p<0.001$) and strongly correlated with the A control score (rho=0.829), the B control score (rho=0.767), the C control score (rho=0.744) and the D control score (rho=0.994).

At the initial measurements, the results of the Schirmer I values have a statistical significance. At OD, the average values of the Schirmer test are 17.31 in the morning and 16.21 in the evening, and at OS the average values are 17.25 in the morning and 15.96 in the evening. Post-treatment measurements indicate an increase in the average Schirmer I test values in both eyes. The differences are significant (Friedman test, $p < 0.001$). For comparisons made between the 3 moments of the measurements, Wilcoxon Signed Ranks Test was used, $p < 0.001$.

In the evening the values decrease significantly compared to the morning, and at one month they increase significantly compared to the morning and evening. Statistical differences between initial and post-treatment Schirmer I values show that local treatment with artificial tears can significantly improve the quality of life of patients with dry eyes, regardless of its severity.

Tear break-up time measurement is a method of determining tear film stability and checking evaporation dry eye syndrome.

The T-BUT values found at OD in the morning have an average of 7.10 seconds, the minimum values found were 3 seconds, and the maximum values were 10 seconds. At OS, the minimum values in the morning were 3 sec., maximum values of 10 sec. and an average of 7.02 sec. At the control performed in the evening, the average values at OD were 4.04 sec., and at OS 3.87sec.

Significant differences between the values found in the morning and evening indicate an increased evaporation of tears from the ocular surface in patients working on the computer for at least 5 hours a day.

After one month of treatment, T-BUT values in both eyes are significantly improved.

The differences are significant (Friedman test, $p<0.001$). In the evening the values decrease significantly compared to the morning (Wilcoxon Signed Ranks Test, $p<0.001$), and at one month of treatment they increase significantly compared to the morning (Wilcoxon Signed Ranks Test, $p=0.002$) and towards the evening (Wilcoxon Signed Ranks Test, $p<0.001$).

PH measurements were performed on each eye. At OD the average Ph is 7.23 in the morning, 7.46 in the evening and 7.14 after a month of treatment. For OS, the average pH values are 7.40 in the morning, 7.73 in the evening and 7.23 post-treatment. The differences are statistically significant (Friedman test, $p < 0.001$). In the evening, the values increase significantly compared to the morning (Wilcoxon Signed Ranks Test, $p < 0.001$), and at one month they decrease significantly compared to the morning (Wilcoxon Signed Ranks Test, $p = 0.007$) and compared to the evening ($p < 0.001$). Thus, there is a slight tendency to alkalize the tear pH in the evening, after a minimum time of 5 hours spent in front of the computer. Also, topical treatment with artificial tears helps to lessen this tendency.

Chapter 10 contains "**Discussions**" regarding the results found in this study and their comparison with the results of other studies in the literature**.**

We analyzed the association between digital screens and the dry eye, the mechanisms of deterioration and therapeutic options, hoping to raise awareness of this entity, to reduce overall morbidity and the economic impact of visual impairment associated with computer work.

In our study, the average computer exposure time was 7.67 hours per day. The initial OSDI score at the one-month control was weakly directly correlated, but insignificant with the number of hours spent at the computer. In the present study it was shown that a use of computer for several hours a day caused the instability of the tear film and an uneven distribution of tears on the eye surface, leading to easy evaporation of tears.

The simultaneous presence of positive clinical tests and dry eye symptoms is all the more suggestive for dry eye the more the symptoms are expressed. For the diagnosis of dry eye, the anamnesis is as important as the clinical examination.

In these studies, tests covering all clinical aspects of dry eye syndrome were chosen: the OSDI questionnaire was used to assess symptoms, tear break-up time revealed tear film stability, Schirmer I test measured basal and reflex tear secretion, the tear pH which shows us a slight alkalization of the tears in the SOU.

T-BUT, which represents the stability of the tear film, proved to be significantly lower after a day spent in front of the computer, compared to the measurements made in the morning. Previous studies have shown that the use of computers causes tears to evaporate, which is attributed to a reduction in the number of blinks and an incomplete blink.

In our study, evening T-BUT correlates significantly, directly and moderately with evening T-BUT (rho = 0.583, p <0.001); and vice versa with mean PH in the evening (rho = -0.524, p <0.001) and with PH in the evening (rho = -0.417, p = 0.002). The lower the T-BUT in the evening, the higher the PH.

The tear pH values found by us show that in the evening the values increase significantly compared to the morning, and at one month they decrease significantly compared to the initial measurements performed in the morning and evening (p <0.001).

Thus, there is a slight tendency to alkalize the tear pH in the evening, after a minimum time of 5 hours spent in front of the computer.

Assessment of symptoms plays an important role in the diagnosis of dry eye syndrome.

The OSDI questionnaire was designed for the rapid assessment of dry eye symptoms.

In the present study, the OSDI questionnaire was a reliable tool in diagnosing dry eye syndrome. The OSDI score was directly and significantly correlated with the scores A, B, C, D both initially and at control. The initially assessed OSDI scores were significantly higher compared to those found at one month post-treatment.

The decreased values of post-treatment OSDI scores in this study demonstrate that dry eye symptoms can be improved by using topical medication with artificial tears. Artificial tears increase the stability of the tear film, reduce surface stress, improve the sensitivity to contrast and optical quality of the corneal surface, increase the quality of life.

We evaluated the results of the Schirmer I test performed without topical anesthesia, which measures basal and reflex tear secretion. This suggests that the SOU in patients the mechanism of evaporation is the main culprit in the presence of Dry Eye Syndrome in computer users. In this study, significant differences were found between morning and evening values. Also, the values of the SCHIRMER I test in the evening correlate inversely and weakly with the pH values in the evening, which indicates that a decreased tear secretion leads to a slight increase in tear pH.

The results obtained in our studies were compared with data from the literature. Following this comparison, we could observe both differences and similarities. A complete comparison is not possible because each study is designed differently, starting from the criteria for inclusion in the study, the diagnostic tests used and the biological reference ranges taken into account.

Chapter 11 contains the final "**Conclusions**" of this study.

The use of the digital screen is part of everyday life and is a risk factor for SOU.

Dry eye syndrome is common among digital screen users, and the mean age in this study was 36.38 years, which shows an increasing predominance of SOU in young patients.

The direct relationship between the use of the digital screen and Dry Eye Syndrome is a low blink rate and an increased percentage of incomplete blinks while using the digital screen. This leads to dryness of the eye surface, which facilitates the development of SOU when individuals are actively involved on digital screens for long periods of time.

In this study, the OSDI questionnaire proved to be a reliable tool for diagnosing Dry Eye Syndrome in people working on the computer, so we conclude that the OSDI questionnaire can be used as a screening tool for dry eye syndrome.

It is also necessary to correlate OSDI values with clinical tests to support the diagnosis of dry eye. Clinical tests commonly used in clinical practice for the diagnosis of dry eye should be easy to perform, non-invasive, but at the same time inexpensive and able to guide the clinician to a correct and complete diagnosis.

In the present study, T-BUT was of significant importance in the diagnosis of Dry Eye Syndrome, demonstrating that the evaporative component is the main form of SOU in patients working in front of the computer.

Slightly altered tear pH values show that there is a slight alkalization of pH in patients with dry eyes, but it cannot be considered as a diagnostic test due to errors that may occur in its performance.

It is important to educate patients about the link between SOU and the use of the digital screen and about strategies for preventing this pathology, as well as initiating appropriate treatment.

Given the decrease in OSDI score A, B, C, D as well as the final OSDI score at one month of treatment, we conclude that treatment with artificial tears can bring significant improvements on dry eye symptoms. Also, the results of the Schirmer I test, T-BUT and tear pH strengthen our conclusion that artificial tears as an initial treatment for SOU are very helpful.

For patients with dry eyes, education on lifestyle changes should be considered. Therefore, for the prevention of SOU we can explain the need for prevention measures for people working on the computer such as: rule 20-20-20, frequent blinking, eye rest after a period spent at the computer, optimizing the humidity in the room.

REFERENCES

1. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, Liu Z, Nelson JD, Nichols JJ, Tsubota K, Stapleton F. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017 Jul;15(3):276-283
2. Lemp MA, Baudouin C, Baum J, Dogru M, Foulks GN, Kinoshita S et al. The definition and classification of dry eye dibronsease: report of the definition and classification Subcommittee of the International Dry Eye Workshop. Ocul Surf 2007; 5(2): 75–92
3. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, Na KS, Schaumberg D, Uchino M, Vehof J, Viso E, Vitale S, Jones L. TFOS DEWS II Epidemiology Report. Ocul Surf. 2017 Jul;15(3):334-365
4. Ranasinghe P, Wathurapatha WS, Perera YS, Lamabadusuriya DA, Kulatunga S, Jayawardana N, et al. Computer vision syndrome among computer office workers in a developing country: an evaluation of prevalence and risk factors. *BMC Res Notes.* 2016;9:150
5. *Izquierdo, Natalio J.; Townsend, William.* "Computer Vision Syndrome". *Medscape Reference: Drugs, Diseases & Procedures. WebMD LLC*. Retrieved 27 February 2012
6. Munshi S, Varghese A, Dhar-Munshi S. Computer vision syndrome-A common cause of unexplained visual symptoms in the modern era. Int J Clin Pract. 2017:71
7. Portello JK, Rosenfield M, Chu CA. Blink rate, incomplete blinks and computer vision syndrome. Optom Vis Sci. 2013;90:482–7
8. Blalock TD, Spurr-Michaud SJ, Tisdale AS, Gipson IK. Release of Membrane –Associated Mucins from Ocular Surface Epithelia. Invest. Ophthalmol. Vis.Sci, 200849(5):1864-1871
9. Basic and clinical science course: orbit, eyelids, and lacrimal system. *American Academy of Ophthalmoloy.* 2012;7:243–244.
10. F. Fodor, Arety Dinulescu, Morfopatologia ochiului și anexelor sale – Aparatul lacrimal, 389 – 391
11. Sherman DD, Gonnering RS, Wallow IH, Lemke BN, Doos WG, Dortzbach RK, Lyon DB, Bindley CD. Identification of orbital lymphatics: enzyme histochemical light microscopic and electron microscopic studies. Ophthalmic Plast Reconstr Surg. 1993;9(3):153-69
12. M. Dumitrache, Tratat de Oftalmologie, Volum I, 2012, pagina 44-47
13. Dartt, Darlene A. "Neural regulation of lacrimal gland secretory processes: relevance in dry eye diseases." *Progress in retinal and eye research* vol. 28,3 (2009): 155-77
14. Obata H. Anatomy and histopathology of the human lacrimal gland. *Cornea.* 2006;25(10, supplement 1):S82–S89
15. Imanishi J., Kamiyama K., Iguchi I., Kita M., Sotozono C., Kinoshita S. Growth factors: importance in wound healing and maintenance of transparency of the cornea. *Progress in Retinal and Eye Research.* 2000;19(1):113–129.
16. Bewes T, Sacks R, Sacks PL, Chin D, Mrad N, Wilcsek G, Tumuluri K, Harvey R. Incidence of neoplasia in patients with unilateral epiphora. J Laryngol Otol. 2015 Jul;129 Suppl 3:S53-7
17. Cochran ML, Aslam S, Czyz CN. Anatomy, Head and Neck, Eye Nasolacrimal. (Updated 2020 Jul 27). In: StatPearls (Internet). Treasure Island (FL): StatPearls Publishing; 2021 Jan-.
18. Yazici A, Bulbul E, Yazici H, Sari E, Tiskaoglu N, Yanik B, Ermis S. Lacrimal Gland Volume Changes in Unilateral Primary Acquired Nasolacrimal Obstruction. Invest Ophthalmol Vis Sci. 2015 Jul;56(8):4425-9.
19. Matsumoto H, Matsumoto A. An Unusual Case of Nasolacrimal Obstruction Caused by Foodstuffs. Case Rep Ophthalmol. 2015 Sep-Dec;6(3):307-10
20. Tamboli DA, Harris MA, Hogg JP, Realini T, Sivak-Callcott JA. Computed tomography dimensions of the lacrimal gland in normal Caucasian orbits. Ophthalmic Plast Reconstr Surg. 2011 Nov-Dec;27(6):453-6
21. M.J.Koos, C. Lehaci – Sindrom Sicca Clinica și terapie, International Book Access 2007, pg. 11-36
22. Millar T. J., Schuett B. S. The real reason for having a meibomian lipid layer covering the outer surface of the tear film—a review. *Experimental Eye Research*. 2015;137:125–138.
23. Szczesna, Dorota & Jaronski, Jaroslaw & Kasprzak, Henryk & Stenevi, Ulf. (2005). Interferometric measurements of the tear film irregularities on the human cornea. 5959. 10.1117/12.622176.)
24. Kunert KS, Keane-Myers AM, Spurr-Michaud S, et al. Aberation in goblet cell numbers and mucin gene expression in a mouse model of allergic conjunctivitis. Invest. Ophthalmol. Vis.Sci.2001, 42:2483-89

25. Methologies to diagnose and monitor dry eye disease: Report of the Diagnostic Methodology Suncommomittee of the International Dry Eye Work Shop(2007). 2007, 5(2): 108-152.
26. McDermott AM. Antimicrobial compounds in tears. *Exp Eye Res*. 2013;117:53-61
27. Danjo Y, Watanabe H, Tisdale AS, George M, Tsumura T, Abelson MB, et al. Alteration of mucin in human conjunctival epithelia in dry eye. *Invest Ophthalmol Vis Sci.* 1998;39:2602–9
28. Klenkler B, Sheardown H, Jones L, 2007. Growth factors in the tear film: role in tissue maintenance, wound healing, and ocular pathology. *The ocular surface* 5, 228–239
29. Georgiev GA, Eftimov P, Yokoi N, 2017. Structure-function relationship of tear film lipid layer: A contemporary perspective. *Experimental eye research* 163, 17–28
30. Cwiklik L, 2016. Tear film lipid layer: A molecular level view. *Biochim Biophys Acta* 1858, 2421–2430
31. Korb DR, Craig J, Doughty M, Guillon J, Smith G, Tomlinson A. The Tear Film: Structure, Function and Clinical Examination. BCLA, 2002).
32. Khurana AK, Chaudhary R, Ahluwalia BK, Gupta S. Tear film profile in dry eye. *Acta Ophthalmol (Copenh)* 1991;69:79–86.
33. Sen DK, Sarin GS. Immunoglobulin concentrations in human tears in ocular diseases. *Br J Ophthalmol*. 1979;63(5):297-300
34. Lamberts DW. Physiology of the tear film In: *The Cornea.* (eds Smolin G, Thoft RA.) Little Brown & Co, New York, 1994; 439–455
35. King-Smith PE, Fink BA, Fogt N *et al.* The thickness of the human precorneal tear film: evidence from reflection spectra. *Investigative Ophthalmology and Visual Science* 2000; 41: 3348–3359
36. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf. 2007 Apr;5(2):75-92
37. Stern ME, Beuerman RW, Fox RI, et al. The pathology of dry eye; the interaction between the ocular surface and lacrimal glands. Cornea 1998;17:584-9
38. Ilene K. Gipson, The Ocular Surface: The Challenge to Enable and Protect Vision, The Friedenwald Lecture Invest. Ophthalmol. Vis.Sci. October 2007 vol.48no.104391-4398
39. Cernea Paul, Tratat de Oftalmologie, Editura medicala Bucuresti 2002: 304-322
40. Schaumb erg DA, Sulliv an DA, Buring JE, Dana MR. Prev alence of dry eye syndrome among US women. Am J Op hthalmo l 2003:136;318-26
41. Lee AJ, Lee J, Saw SM, et al. Prev alence and risk factors associated with dry eye symp toms: a p op ulationb ased study inIndonesia. B rJOp hthalmo l 2002;86:1347-51
42. Lin PY , Tsai SY , Cheng CY , et al. Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shihp ai Eye Study. Ophthalmology 2003;110:1096-101
43. Denoyer A, Rabut G, Baudouin C. Tear film aberration dynamics and vision-related quality of life in patients with dry eye disease. *Ophthalmology.* 2012;119:1811–8
44. Torkildsen G. The effects of lubricant eye drops on visual function as measured by the Inter-blink interval Visual Acuity Decay test. *Clin Ophthalmol.* 2009;3:501–6
45. Argueso P, Spurr-Michaud S, Russo Cl, Tisdale A, Gipson IK.MUC16 mucin is expressed by the human ocularsurface epithelia and carries the H185carbohydrate epitope. Invest Ophthalmol Vis Sci 2003, 44:2487-2495
46. Dastjerdi MH & Dana R (2009): Corneal nerve alterations in dry eye-associated ocular surface disease. *Int Ophthalmol Clin* 49: 11–20
47. Dry Eye WorkShop (2007a): The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop. *Ocul Surf* 5: 75–92
48. Bourcier T, Acosta MC, Borderie V, Borras F, Gallar J, Bury T, Laroche L & Belmonte C (2005): Decreased corneal sensitivity in patients with dry eye. *Invest Ophthalmol Vis Sci* 46: 2341–2345
49. , M'Garrech M, Rousseau A, Kaswin G, Sauer A, Barreau E, Bourcier T & Labetoulle M (2013): Impairment of lacrimal secretion in the unaffected fellow eye of patients with recurrent unilateral herpetic keratitis. *Ophthalmology* 120: 1959–1967
50. Rolando M, Barabino S, Mingari C, Moretti S, Giuffrida S & Calabria G (2005): Distribution of conjunctival HLA-DR expression and the pathogenesis of damage in early dry eyes. *Cornea* 24: 951–954
51. , Mantelli F, Micera A, Sacchetti M & Bonini S (2010): Neurogenic inflammation of the ocular surface. *Curr Opin Allergy Clin Immunol* 10: 498–504)
52. Luo L, Li DQ, Doshi A, Farley W, Pflugfelder SC. Experimental dry eye induced expression of inflammatory cytokines (IL-1α and TNF-α), MMP-9 and activated MAPK by the corneal epithelium. Invest Ophthalmol. Vis Sci.2003, 44:E Abstract 1026.
53. Luo L, Li DQ, Doshi A, Farley W, Corrales RM & Pflugfelder SC (2004): Experimental dry eye stimulates production of inflammatory cytokines and MMP-9 and activates MAPK signaling pathways on the ocular surface. *Invest Ophthalmol Vis Sci* 45: 4293–4301

54. Pflugfelder SC, de Paiva CS, Li DQ & Stern ME (2008a): Epithelial-immune cell interaction in dry eye. *Cornea* 27(Suppl 1): S9–S11

55. Siemasko KF, Gao J, Calder VL, Hanna R, Calonge M, Pflugfelder SC, Niederkorn JY & Stern ME (2008): In vitro expanded $CD4^+CD25^+Foxp3^+$ regulatory T cells maintain a normal phenotype and suppress immune-mediated ocular surface inflammation. *Invest Ophthalmol Vis Sci* 49: 5434–5440

56. ., Luo L, Li DQ & Pflugfelder SC (2007): Hyperosmolarity-induced apoptosis in human corneal epithelial cells is mediated by cytochrome c and MAPK pathways. *Cornea* 26: 452–460, Gao J, Sana R, Calder V, Calonge M, Lee W, Wheeler LA & Stern ME (2013): Mitochondrial permeability transition pore in inflammatory apoptosis of human conjunctival epithelial cells and T cells: effect of cyclosporin A. *Invest Ophthalmol Vis Sci* 54: 4717–4733

57. Tsubota K, Yokoi N, Watanabe H, et al. A New Perspective on Dry Eye Classification: Proposal by the Asia Dry Eye Society (published correction appears in Eye Contact Lens. 2020 Sep;46(5):e39). *Eye Contact Lens*. 2020;46 Suppl 1(1):S2-S13. doi:10.1097/ICL.0000000000000643

58. Christodoulou MI, Kapsogeorgou EK, Moutsopoulos HM. Characteristics of the minor salivary gland infiltrates in Sjogren's syndrome. *J Autoimmun.* 2010;34(4):400–407

59. Garcia-Carrasco M, Ramos-Casals M, Rosas J, et al. Primary Sjogren syndrome: clinical and immunologic disease patterns in a cohort of 400 patients. *Medicine (Baltimore)* 2002;81(4):270–280

60. M. Dumitrache, Tratat de Oftalmologie, Volum I, 2012, pagina 474-477

61. Findlay Q, Reid K. Dry eye disease: when to treat and when to refer. *Aust Prescr*. 2018;41(5):160-163

62. Sommer A, West KP. *Vitamin A Deficiency: Health, Survival and Vision.* New York: Oxford University Press; 1995)

63. Zeba AN, Sorgho H, Rouamba N, et al. Major reduction of malaria morbidity with combined vitamin A and zinc supplementation in young children in Burkina Faso: a randomized double blind trial. *Nutr J*. 2008;7(1):7.

64. Peck T, Olsakovsky L, Aggarwal S. Dry eye syndrome in menopause and perimenopausal age group. *J Midlife Health* 2017;8:51-4. 10.4103/jmh.JMH_41_17

65. Okumura, Y.; Inomata, T.; Iwata, N.; Sung, J.; Fujimoto, K.; Fujio, K.; Midorikawa-Inomata, A.; Miura, M.; Akasaki, Y.; Murakami, A. A Review of Dry Eye Questionnaires: Measuring Patient-Reported Outcomes and Health-Related Quality of Life. *Diagnostics* 2020, *10*, 559.

66. Stevens S. Schirmer's test. Community Eye Health. 2011 Dec;24(76):45

67. Cho P. Schirmer Test. I. A Review. *Optom Vis Sci.* 1993;70(2):152–156. doi: 10.1097/00006324-199302000-00011

68. Senchyna M, Wax MB. Quantitative assessment of tear production: A review of methods and utility in dry eye drug discovery. *J Ocul Biol Dis Infor*. 2008;1(1):1-6. doi:10.1007/s12177-008-9006-2).

69. Sakamoto R, et al. The phenol red thread tear test: A cross cultural study. *Invest Ophthalmol Vis Sci.* 1993;34:3510–3514

70. Tomlinson A, Khanal S. Assessment of tear film dynamics: Quantification Approach. *Ocul Surf.* 2005;3:81–85. , Macri A, Plugfelder S. Correlation of the Schirmer I and fluorescein clearance tests with the severity of corneal epithelial and eyelid disease. *Arch Ophthalmol.* 2000;118:1632–1638.).

71. Stanila A. O noua abordare a sindromului de ochi uscat, stabiliyarea filmului lacrimal. Acta Medica Transilvanica. 2010, 1(2): 39-41.

72. Tomlinson A, Khanal S, Ramaesh K, Diaper C, McFadyen A. Tear film osmolarity: Determination of a referent for dry eye diagnosis. Invest Ophthalmol Vis sci.2006, 47: 4309-15

73. Tomlinson A, McCann LC, Pearce EI. Comparison of human tear film osmolarity measured by electrical impedance and freezing point depression techniques. *Cornea.* 2010;29(9):1036–1041

74. Gokhale M, Stahl U, Jalbert I. In situ osmometry: validation and effect of sample collection technique. *Optom Vis Sci.* 2013;90(4):359–365

75. Feenstra RPF, Tseng SCG. Comparation of fluorescein and rose Bengal staining. Ophthalmology. 1992, 92:605-617
76. Kim J. The use of vital dyes in corneal disease. *Curr Opin Ophthalmol.* 2000;11:241–247
77. Chodosh J, Dix RD, Howell RC, Stroop WG, Tseng SC. Staining characteristics and antiviral activity of sulforhodamine B and lissamine green B. *Invest Ophthalmol Vis Sci.* 1994;35:1046–1058
78. Roh JH Chi MJ. Efficacy of dye disappearance test and tear meniscus height in diagnosis and postoperative assessment of nasolacrimal duct obstruction. *Acta Ophthalmol*. 2010; 88: 73–77
79. Lee JH, Kee CW. The significance of tear film break-up time in the diagnosis of dry eye syndrome. *Korean J Ophthalmol.* 1988;2:69–71
80. Farnaud S, Evans RW. Lactoferrin – a multifunctional protein with antimicrobial properties. *Mol Immunol*. 2003 Nov;40(7):395-405
81. Karns K, Herr AE. Human tear protein analysis enabled by an alkaline microfluidic homogeneous immunoassay. *Anal Chem*. 2011 Nov 1;83(21):8115-8122
82. Da Dalt S, Moncada A, Priori R, Valesini G, Pivetti-Pezzi P. The lactoferrin tear test in the diagnosis of Sjögren's syndrome. Eur J Ophthalmol. 1996 Jul-Sep;6(3):284-6. PMID: 8908435
83. Berra M, Galperín G, Berra F, Marquez MI, Mandaradoni M, Tau J, Berra A. Tear Lysozyme in Sjögren´s syndrome, Meibomian gland dysfunction, and non-dry-eye. Arq Bras Oftalmol. 2021 Aug 18:S0004-27492021005005220
84. Natadisastra G, Wittpenn JR, West KP Jr, Muhilal, Sommer A. Impression cytology for detection of vitamin A deficiency. Arch Ophthalmol. 1987 Sep;105(9):1224-8
85. Nelson JD, Havener VR, Cameron JD. Cellulose acetate impressions of the ocular surface. Dry eye states. Arch Ophthalmol. 1983 Dec;101(12):1869-72
86. Tseng SC. Staging of conjunctival squamous metaplasia by impression cytology. Ophthalmology. 1985 Jun;92(6):728-33.)
87. Wittpenn JR, Tseng SC, Sommer A. Detection of early xerophthalmia by impression cytology. Arch Ophthalmol. 1986 Feb;104(2):237-9).
88. Rolando M: Tear mucus ferning test in normal and keratoconjunctivitis sicca eyes. Chibret Int J Ophthalmol 1984;2(4):32-41
89. Masmali AM, Purslow C, Murphy PJ. The tear ferning test: a simple clinical technique to evaluate the ocular tear film. Clin Exp Optom. 2014 Sep;97(5):399-406
90. Tabbara K., Okumoto M. Ocular ferning test: a qualitative test for mucus deficiency. *Ophthalmology.* 1982;89:712–714
91. Horwath J., Ettinger K., Bachernegg M., Bodner E., Schmut O. Ocular Ferning test – effect of temperature and humidity on tear Ferning patterns. *Ophthalmologica.* 2001;215:102–107
92. Golding T.R., Brennan N.A. The basis of tear ferning. *Clin Exp Ophthalmol.* 1989;72:102–112
93. Chew CKS, Jansweijer C, Tiffany JM, et al. (1993a). An instrument for quantifying meibomian lipid on the lid margin: the Meibometer. Curr Eye Res 12:247-54
94. Komuro A, Yokoi N, Kinoshita S, et al. (2002.Assessment of meibomian gland function by a newly developed laser meibometer. Adv Exp Med Biol 506:517-20
95. Fujishima H, Yagi Y, Toda I, Tsubota K. Quantitative evaluation of post-surgical inflammation by infra-red radiation thermometer and laser flare-cell meter. J7 Cataract Refract Surg 1994; 20: 451-4.)
96. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007) *Ocul Surf.* 2007;5:163–178
97. Şimşek C, Doğru M, Kojima T, Tsubota K. Current Management and Treatment of Dry Eye Disease. *Turk J Ophthalmol*. 2018;48(6):309-313
98. Barabino S, Rolando M, Nardi M, et al. The effect of an artificial tear combining hyaluronic acid and tamarind seeds polysaccharide in patients with moderate dry eye syndrome: a new treatment for dry eye. *Eur J Ophthalmol.* 2014;24:173–178
99. Cohen S, Martin A, Sall K. Evaluation of clinical outcomes in patients with dry eye disease using lubricant eye drops containing polyethylene glycol or carboxymethylcellulose. *Clin Ophthalmol.* 2014;8:157–164
100. Management and therapy of dry eye disease: report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007) *Ocul Surf.* 2007;5:163–178
101. Misawa M, Ohmori S, Yanaura S. Effects of bromhexine on the secretions of saliva and tears. Jpn J Pharmacol. 1985 Oct;39(2):241-50. doi: 10.1254/jjp.39.241. PMID: 4087569
102. Absolon MJ, Brown CA. Acetylcysteine in kerato-conjunctivitis sicca. *Br J Ophthalmol*. 1968;52(4):310-316. doi:10.1136/bjo.52.4.310
103. Nepp J, Knoetzl W, Prinz A, Hoeller S, Prinz M. Management of moderate-to-severe dry eye disease using chitosan-N-acetylcysteine (Lacrimera®) eye drops: a retrospective case series. *Int Ophthalmol*. 2020;40(6):1547-1552. doi:10.1007/s10792-020-01324-5
104. Kentaro Senba, Tatsuro MIyamoto, Hiroshi Eguchi, Yoshinori Mitamura; The Efficacy Of Oral Pilocarpine For The Treatment Of Dry Eye Symptoms In Patients With Aqueous Tear Deficiency And Evaporative Dry Eye. *Invest. Ophthalmol. Vis. Sci.* 2011;52(14):3837

105. Kawakita T, Shimmura S, Tsubota K. Effect of Oral Pilocarpine in Treating Severe Dry Eye in Patients With Sjögren Syndrome. Asia Pac J Ophthalmol (Phila). 2015 Mar-Apr;4(2):101-5. doi: 10.1097/APO.0000000000000040. PMID: 26065354.)
106. Pflugfelder SC. Antiinflammatory therapy for dry eye. Am J Ophthalmol. 2004 Feb;137(2):337-42. doi: 10.1016/j.ajo.2003.10.036. PMID: 14962426
107. DeNaeyer G, Sanders DR, Farajian TS. Surface coverage with single vs. multiple gaze surface topography to fit scleral lenses. *Cont Lens Anterior Eye.* 2017;40:162–169
108. Van der Worp E. *A Guide to Scleral Lens Fitting.* 2nd ed. Forest Grove, OR: Pacific University; 2015
109. Harthan JS, Shorter E. Therapeutic uses of scleral contact lenses for ocular surface disease: patient selection and special considerations. *Clin Optom (Auckl)*. 2018;10:65-74. Published 2018 Jul 11. doi:10.2147/OPTO.S144357
110. Ogawa M, Dogru M, Toriyama N, Yamaguchi T, Shimazaki J, Tsubota K. Evaluation of the Effect of Moist Chamber Spectacles in Patients With Dry Eye Exposed to Adverse Environment Conditions. Eye Contact Lens. 2018 Nov;44(6):379-383
111. Tai 2002. Tai MC, Cosar CB, Cohen EJ, Rapuano CJ, Laibson PR. The clinical efficacy of silicone punctal plug therapy. *Cornea.* 2002;21(2):135–9
112. Maguire L. J., Bartley G. B. Complications associated with the new smaller size freeman punctal plug. *Archives of Ophthalmology.* 1989;107(7):961–962. doi: 10.1001/archopht.1989.01070020023015
113. Taban M., Chen B., Perry J. D. Update on punctal plugs. *Comprehensive Ophthalmology Update.* 2006;7(5):205–212
114. Yaguchi S., Ogawa Y., Kamoi M., et al. Surgical management of lacrimal punctal cauterization in chronic GVHD-related dry eye with recurrent punctal plug extrusion. *Bone Marrow Transplantation.* 2012;47(11):1465–1469. doi: 10.1038/bmt.2012.50
115. Murube-del-Castillo J, Hernandez-King J. Treatment of dry eye by moving the lacrimal punctum to dry dock. Ophthalmic Surg. 1993 Jan;24(1):53-8. PMID: 8446336.
116. Murube J, Németh J, et al. The triple classification of dry eye for practical clinical use. *Eur J Ophthalmol*. 2005;15(6):660-667
117. Macaluso DC, Feldman STKrachmer JH, Mannis MJ, Holland EJ. Pathogenesis of sterile corneal erosions and ulcerations Cornea. 1997;1 St. Louis Mosby:199–212
118. Cosar CB, Cohen EJ, Rapuano CJ, Maus M, Penne RP, Flanagan JC, Laibson PR. Tarsorrhaphy: clinical experience from a cornea practice. Cornea. 2001 Nov;20(8):787-91.
119. King-Smith PE, Fink BA, Fogt N, Nichols KK, Hill RM, Wilson GS. The thickness of the human precorneal tear film: evidence from reflection spectra. Invest Ophthalmol Vis Sci. 2000 Oct;41(11):3348-59
120. Willcox MDP, Argüeso P, Georgiev GA, Holopainen JM, Laurie GW, Millar TJ, Papas EB, Rolland JP, Schmidt TA, Stahl U, Suarez T, Subbaraman LN, Uçakhan OÖ, Jones L. TFOS DEWS II Tear Film Report. Ocul Surf. 2017 Jul;15(3):366-403
121. O'Neil EC, Henderson M, Massaro-Giordano M, Bunya VY. Advances in dry eye disease treatment. Curr Opin Ophthalmol. 2019 May;30(3):166-178
122. Lemp MA, Crews LA, Bron AJ, Foulks GN, Sullivan BD. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. *Cornea.* 2012;31:472–478
123. Ohashi Y, Ishida R, Kojima T, Goto E, Matsumoto Y, Watanabe K, et al. Abnormal protein profiles in tears with dry eye syndrome. *Am J Ophthalmol.* 2003;136:291–299
124. Bron AJ, Tomlinson A, Foulks GN, et al. Rethinking dry eEye disease: A perspective on clinical implications. *Ocul Surf.* 2014;12:1–31
125. Ridder WH, Zhang Y, Huang JF. Evaluation of reading speed and contrast sensitivity in dry eye disease. *Optom Vis Sci.* (3rd) 2013;90:37–44
126. Deschamps N, Ricaud X, Rabut G, Labbe A, Baudouin C, Denoyer A. The impact of dry eye disease on visual performance while driving. *Am J Ophthalmol.* 2013;156:184–189
127. Li M, Gong L, Chapin WJ, Zhu M. Assessment of vision-related quality of life in dry eye patients. *Invest Ophthalmol Vis Sci.* 2012;53:5722–5727
128. Schiffman RM, Walt JG, Jacobsen G, Doyle JJ, Lebovics G, Sumner W. Utility assessment among patients with dry eye disease. *Ophthalmology.* 2003;110:1412–1419
129. Paulsen AJ, Cruickshanks KJ, Fischer ME, et al. Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life. *Am J Ophthalmol.* 2014;157:799–806
130. Solomon A, Dursun D, Liu Z, Xie Y, Macri A, Pflugfelder SC. Pro- and anti-inflammatory forms of interleukin-1 in the tear fluid and conjunctiva of patients with dry-eye disease. *Invest Ophthalmol Vis Sci.* 2001;42:2283–2292
131. Tishler M, Yaron I, Geyer O, Shirazi I, Naftaliev E, Yaron M. Elevated tear interleukin-6 levels in patients with Sjögren syndrome. *Ophthalmology.* 1998;105:2327–2329
132. Foulks GN, Bron AJ. Meibomian gland dysfunction: a clinical scheme for description, diagnosis, classification, and grading. *Ocul Surf.* 2003;1:107–126

133. Messmer EM. The pathophysiology, diagnosis, and treatment of dry eye disease. *Dtsch Arztebl Int*. 2015;112(5):71-82
134. Inagaki E, Ogawa Y, Matsumoto Y, et al. Four cases of corneal perforation in patients with chronic graft-versus-host disease. *Mol Vis.* 2011;17:598–606
135. Messmer EM, Hoops JP, Kampik A. Bilateral recurrent calcareous degeneration of the cornea. *Cornea.* 2005;24:498–502
136. Stevenson W, Shikari H, Saboo US, Amparo F, Dana R. Bilateral corneal ulceration in ocular graft-versus-host disease. *Clin Ophthalmol.* 2013;7:2153–2158
137. Turgut B, Aydemir O, Kaya M, et al. Spontaneous corneal perforation in a patient with lamellar ichthyosis and dry eye. *Clin Ophthalmol.* 2009;3:611–613
138. Bergqvist UO, Knave BG. Eye discomfort and work with visual display terminals. *Scand J Work Environ Health.* 1994;20(1):27–33
139. Computer vision syndrome among computer office workers in a developing country: an evaluation of prevalence and risk factors. Ranasinghe P, Wathurapatha WS, Perera YS, Lamabadusuriya DA, Kulatunga S, Jayawardana N, Katulanda P. *BMC Res Notes.* 2016;9:150
140. Charpe N. A., Kaushik V. Computer vision syndrome (CVS): recognition and control in software professionals. *Journal of Human Ecology*. 2009;28(1):67–69
141. Wimalasundera S. Computer vision syndrome. *Galle Medical Journal*. 2006;11(1):25–29
142. Tadesse S., Kelaye T., Assefa Y. Utilization of personal protective equipment and associated factors among textile factory workers at Hawassa Town, Southern Ethiopia. *Journal of Occupational Medicine and Toxicology*. 2016;11(1):1–6
143. Kozeis N. Impact of computer use on children's vision. *Hippokratia.* 2009;13(4):230–231
144. Gajta A.,Jurca A.,Stănilă A. and Stănilă D. (2021) The effects of microwave radiation generated by mobile phones on the tear film. Revista Romana de Medicina de Laborator, Vol.29 (Issue 3), pp. 277-286
145. Gangamma M. P., Poonam, Rajagopala M. A clinical study on "computer vision syndrome" and its management with Triphala eye drops and Saptamrita Lauha. *AYU (An International Quarterly Journal of Research in Ayurveda)* 2010;31(2):236–239
146. Schiffman RM. Reliability and Validity of the Ocular Surface Disease Index. *Archives of Ophthalmology.* 2000;*118*(5):615-621
147. Walt JG, Rowe MM, Stern KL. Evaluating the functional impact of dry eye: The Ocular Surface Disease Index. *Drug Inf J.* 1997;31:1436
148. Grubbs JR, Tolleson-Rinehart S, Huynh K, Davis RM. A Review of Quality of Life Measures in Dry Eye Questionnaires. *Cornea.* 2014;*33*(2):215-218
149. Özcura F, Aydin S, Helvaci MR. Ocular Surface Disease Index for the Diagnosis of Dry Eye Syndrome. *Ocular Immunology and Inflammation.* 2007;*15*(5):389-393
150. Holly FJ, Lamberts DW, Esquivel ED. Kinetics of capillary tear flow in the Schirmer strip. Curr Eye Res. 1982;2(1):57-70
151. Miyake H, Kawano Y, Tanaka H, Iwata A, Imanaka T, Nakamura M. Tear volume estimation using a modified Schirmer test: a randomized, multicenter, double-blind trial comparing 3% diquafosol ophthalmic solution and artificial tears in dry eye patients. Clin Ophthalmol. 2016 May 13;10:879-86
152. Tomlinson A, Blades KJ, Pearce EI. What does the phenol red thread test actually measure? *Optom Vis Sci.* 2001;78:142–146
153. Nelson PS. A shorter Schirmer test. *Optom Mon.* 1982;73:568–569
154. Bawazeer AM, Hodge WG. One minute Schirmer test with anesthetic. *Cornea.* 2003;22:285–287.
155. Abelson MB, Ousler GW, 3rd, Nally LA, Welch D, Krenzer K. Alternative reference values for tear film break up time in normal and dry eye populations. *AdvExp Med Biol.* 2002;506:1121–1125
156. Nichols JJ, Nichols KK, Puent B, Saracino M, Mitchell GL. Evaluation of tear film interference patterns and measures of tear break-up time. *Optom Vis Sci.* 2002;79:363–369
157. Norn MS. Tear fluid pH in normals, contact lens wearers, and pathological cases. *Acta Ophthalmol (Copenh)* 1988;66:485–9
158. Aya K.L., Stern R. Hyaluronan in wound healing: Rediscovering a major player. *Wound Repair Regen.* 2014;22:579–593
159. Aragona P., Papa V., Micali A., Santocono M., Milazzo G. Long term treatment with sodium hyaluronate-containing artificial tears reduces ocular surface damage in patients with dry eye. *Br. J. Ophthalmol.* 2002;86:181–18
160. Jiang D., Liang J., Noble P.W. Hyaluronan as an immune regulator in human diseases. *Physiol. Rev.* 2011;91:221–264
161. Delmage J.M., Powars D.R., Jaynes P.K., Allerton S.E. The selective suppression of immunogenicity by hyaluronic acid. *Ann. Clin. Lab. Sci.* 1986;16:303–310
162. Litwiniuk M., Krejner A., Speyrer M.S., Gauto A.R., Grzela T. Hyaluronic Acid in Inflammation and Tissue Regeneration. *Wounds.* 2016;28:78–88

163. Beck R., Stachs O., Koschmieder A., Mueller-Lierheim W.G.K., Peschel S., van Setten G.B. Hyaluronic Acid as an Alternative to Autologous Human Serum Eye Drops: Initial Clinical Results with High-Molecular-Weight Hyaluronic Acid Eye Drops. *Case Rep. Ophthalmol.* 2019;10:244–255.
164. Costanza MA. Visual and ocular symptoms related to the use of video display terminals. *J Behav Optom.* 1994;5:31–36
165. Uchino M, Schaumberg DA, Dogru M, et al. Prevalence of dry eye disease among Japanese visual display terminal users. *Ophthalmology.* 2008;115(11):1982–1988.
166. Logaraj M, Madhupriya V, Hegde S. Computer vision syndrome and associated factors among medical and engineering students in Chennai. *Ann Med Health Sci Res.* 2014;4(2):179–85
167. Reddy SC, Low CK, Lim YP, Low LL, Mardina F, Nursaleha MP. Computer vision syndrome: a study of knowledge and practices in university students. *Nepal J Ophthalmol.* 2013;5(2):161–8
168. Aronsson G, Strömberg A. Work content and eye discomfort in VDT work. *Int J Occup Saf Ergon*. 1995;1995(1):1–13
169. Hirota M, Uozato H, Kawamorita T, Shibata Y, Yamamoto S. Effect of incomplete blinking on tear film stability. *Optom Vis Sci.* 2013;90:650–7
170. Tribley J, McClain S, Karbasi A, Kaldenberg J. Tips for computer vision syndrome relief and prevention. *Work.* 2011;39:85–7
171. Randolph SA. Computer Vision Syndrome. *Workplace Health Saf.* 2017;65:328
172. Carney LG, Hill RM. Human tear pH. Diurnal variations. *Arch phthalmol.* 1976;94:821–4
173. Coles WH, Jaros PA. Dynamics of ocular surface pH. *Br J Ophthalmol.* 1984;68:549–52
174. Fischer FH, Wiederholt M. Human precorneal tear film pH measured by microelectrodes. *Graefes Arch Clin Exp Ophthalmol.* 1982;218:168–70
175. Bayhan HA, Bayhan SA, Muhafız E, Gürdal C. Evaluation of the Dry Eye Parameters and Tear Osmolarity in Computer Users. *Turkiye Klinikleri J Ophthalmol.* 2014;23:167–71
176. Celebi AR, Ulusoy C, Mirza GE. The efficacy of autologous serum eye drops for severe dry eye syndrome: a randomized double-blind crossover study. *Graefes Arch Clin Exp Ophthalmol.* 2014;252:619–626
177. Akkaya S, Atakan T, Acikalin B, Aksoy S, Ozkurt Y. Effects of long-term computer use on eye dryness. *North Clin Istanb*. 2018;5(4):319-322. Published 2018 Aug 8.